REMARKS

Claims 1-4, 7-8 and 13-16 are pending in the instant application. Claims 1, 8 and 13 are independent. Applicants amended claim 2 to clarify the structures. Table B, on page 14a provides support for the structures in amended claim 2. Applicants have added claims 13-16 directed toward steroidal compounds. Claims 13-16 are supported by original claims 1-4. Applicants have not raised any issues of new matter.

Applicants wish to thank Examiner Jiang for having an Interview to discuss the instant application. Applicants believe the interview was both informative and successful. The amendments and arguments presented flow directly from the Interview of November 15, 2004.

Issue Under 35 U.S.C. §112

Claim 2 stands rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite. The Examiner asserts that the structures in claim 2 are not completely clear.

Applicants have amended the claims as discussed in the Interview of November 15, 2005. The amended claims clearly show where the side-chain attaches to the core structure.

Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph rejection.

Issue Under 35 U.S.C. §102(b)

Claim 2 stands rejected under 35 U.S.C. §102(b) as being anticipated by Lobaccaro et al. (J. Med. Chem., 1997, 40, 2217-2227).

During the Interview of November 15, 2005, Applicants pointed out that claim 2 did not claim a "butyl" group as asserted by the Examiner. Lobaccaro et al. discloses a "butyl" group. The amended structures clearly show that claim 2 does not claim a "butyl" group; therefore, no anticipation exists.

Applicants respectfully request withdrawal of the 35 U.S.C. §102(b) rejection.

Issue Under 35 U.S.C. §103(a)

Claims 1, 3-4 and 7-18 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Lobaccaro et al. (J. Med. Chem., 1997, 40, 2217-2227). Applicants assert that patentable distinctions exist between the present invention and Lobaccaro et al.

Distinctions Between the Present Invention and Lobaccaro et al.

Lobaccaro et al. discloses that the 11β position of the steroid in intermediate compounds 5a-b is substituted with either an ethenyl or a butenyl chain. *See Scheme 1, page 2218.* Scheme 3, page 2219 of Lobaccaro et al. discloses that the 11β position of the steroid has a linear C10 chain substituted with a terminal tosylate group, i.e. compound 20. Lobaccaro et al., however, do not disclose any unsubstituted 11β-alkyl derivatives (see also the first full sentence of the Abstract, i.e. '11β-methyl, 11β-butyl, or 11β-decyl derivatives bearing an 11β-terminal electrophilic functionality').

Lobaccaro et al. fails to disclose a steroid compound of formula I, wherein R_{11} is a hydrocarbon group which may be linear, or branched comprising one singular linear chain having a length of from 5 to 9 carbon atoms as the longest chain. The Examiner asserts that compounds 5a-b in Scheme 1 of Lobaccaro et al. render the present invention obvious because the alkyl chains at the 11 position are homologs. Applicants have asserted that Lobaccaro et al. fails to disclose a steroid with an 11β-alkyl chain having ten carbons. Lobaccaro et al. only discloses a tosylate-substituted decyl chain. *See Scheme 3.* Therefore, Lobaccaro et al. fails to disclose a homolog of an alkyl C9 chain.

As previously presented in a response, Lobaccaro et al. only discloses an 11β-alkyl chain without any longer chains than four carbon atoms; thus, a skilled artisan would not be motivated to make the claimed compounds having 5-9 carbons in chain length.

Applicants will discuss the unexpected results in greater detail below in describing the attached 37 C.F.R. §1.132 Declaration.

Therefore, Applicants respectfully submit that a *prima facie* case of obviousness has not been presented and therefore, request withdrawal of the 35 U.S.C. §103(a) rejection.

Issue Under 35 U.S.C. §103(a)

Claims 1, 3-4 and 7-8 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Napolitano et al. (J. Med. Chem., 1995, 38, 2774-2779). Applicants assert that patentable distinctions exist between the present invention and Napolitano et al.

Distinctions Between the Present Invention and Napolitano et al.

Napolitano et al. discloses that the 11β position of the steroid is substituted or unsubstituted short chain alkyl groups

(less than five carbon atoms). In Table I, page 2776, Napolitano et al exclusively recites alkyl chains of 2 to 4 carbons in length. However, the Examiner asserts that a skilled artisan would be motivated to extend the carbon chain and expect similar results.

Applicants claim a specific range for the chain length at the 11β position. Applicants assert that unexpected results show that this specific range identifies a series of compounds that have a specific agonist and antagonist profile, which a skilled artisan would not have known. Therefore, any argument of obviousness is overcome because a skilled artisan would not have had a reasonable expectation of success of achieving the selectivity of the present invention. See below for a more detailed explanation of the unexpected results.

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

Unexpected Results

Applicants assert that a *prima facie* case of obviousness has not been established. However, if the Examiner maintains that a proper *prima facie* case of obviousness exists; Applicants present the following data and arguments that unexpected results are present.

In reference to the Examiner's remark 'therefore whether the compounds herein are estrogen receptor subtypes α or β and different effects as ERα agonist activity and ERβ antagonist are not deemed to be an essential and critical element of the claimed invention'. The mixed estrogen-receptor profile of the compounds according to the present invention, makes them suitable as improved estrogens, in the sense that they can be used in estrogen-related disorders, such as menopausal complaints and osteoporosis, and in contraception, and further may also be suitable in the treatment or prevention of Alzheimer's disease, breast tumor, benign prostate hypertrophy, and cardiovascular disorders. The preferred compounds of the invention, which have a marked ERα agonistic and ERβ antagonistic profile, are particularly suitable in the treatment and prevention of estrogen-deficiency related disorders under diminished estrogen-related side-effects. The strongly ERβ antagonistic compounds of the invention can also have a utility in the treatment and prevention of endometriosis and other estrogen-related disorders. Furthermore, "since these receptors (ERα and β) have a different distribution in human tissue, the finding of compounds which possess a selective affinity for either of the two is an important technical progress making it possible to provide a more selective treatment of estrogen

deficiency related disorders with a lower burden of estrogen related side-effects" (Specification page 1, lines 21 to 25).

Compounds identified in the prior art which are either full agonists at both estrogen receptor subtypes (as we have shown with some of the prior art compounds) or full antagonists at both estrogen receptor subtypes simply fail to achieve this objective.

Applicants' invention resides in a very specific finding (stated clearly in the declaration),i.e. crossover from estrogen receptor agonist to antagonist occurs with different C-11 chain lengths at the different receptor subtypes α and β making it possible to find compounds which are ERα agonists and ERβ antagonists. The cited prior art fails to appreciate this significant discovery; thus, neither of the cited documents allow a skilled person to learn anything about requirements for selectivity at either of the estrogen receptor subtypes from information in the prior art. The most the skilled person can conclude is an invitation to experiment that one can achieve a change going from estrogen agonist to antagonist at higher C-11 chain lengths (from Lobaccaro et. al.). The skilled person would not conclude that the possibility exists to find compounds which are agonist at one type and antagonist at the other let alone at the chain length at which it is possible.

As discussed during the interview of November 15, 2004, compounds 3, 5, 6, 8 and 11 in Table A, which are compounds of the present invention, are agonist at ER-α receptor and antagonist at ER-β receptor. Compounds 1, 2, 4, 7 and 9-10 in Table A are agonist at both ER-α and ER-β.

Compounds 4 (1-butynyl) and 5 (2-pentynyl) only differ by one carbon atom in the side chain at position 11, yet 4 is an agonist at ER-β and 5 is an antagonist at ER-β. The same can be said for the difference in compounds 10 and 11.

Please note that compound 2 in Tables A and B is equal to compound 5b of Lobaccaro et al. So, Applicants have a direct comparison of compound 3, present invention representative, with the closest possible prior art homolog compound 2 (i.e. compound 5b of Lobaccaro et al.).

Applicants further have even better comparative data in the application with respect to the compounds disclosed in Napolitano et al., i.e. compound 4 in Table B (carrying a 3-butynyl group, i.e. 4 carbon atoms) is closer to compounds 5 and 6 in accordance with the present invention than compound 2a of Napolitano et al. carrying a 1-propynyl-substituent (i.e. 3 carbon atoms) or compound 3a carrying an 11β-ethynyl group (i.e. 2 carbon atoms). Note that compounds 1a, 1b, 4a, 4b of

Napolitano et al. are electrophilic functionalized affinity labels for the ER.

Applicants have previously presented a 37 C.F.R. §1.132 Declaration where Mr. Antwan Ederveen declares that the series of compounds claimed within the present application are agonist at ER-α and antagonist at ER-β. In a comparison with compounds from the cited prior art, the Declarant concludes that substantially similar compounds produced different functional effects at both estrogen receptor subtypes α and β. Compounds 2 and 3 only differ by one carbon in the side chain at position 11, yet 2 is an agonist ER-β and 3 is an antagonist at ER-β.

The Declarant resubmits that the homologues demonstrate different results that are unexpected and do not follow the teachings of either Lobaccaro et al. or Napolitano et al., which only ER affinity was studied using a cytosolic ER and no reference was made to whether this is the ERα or the ERβ receptor. For this reason alone, neither Napolitano et al. nor Lobaccaro et al. could have suggested the presently claimed mixed protile steroidal compounds.

During the Interview of November 15, 2005, Applicants' representative and the Examiner carefully went through the Declaration and the Tables in the specification.

Applicants have reintroduced the compounds claims because an unexpected pharmaceutically relevant result is significant toward overcoming a *prima facie* case of obviousness for composition claims and compound claims. A difference in antagonism or agonism at the ER-β receptor is pharmaceutically relevant, as discussed above.

Applicants believe they have presented sufficient data to support an unexpected result claim. Applicants assert the instant claims are patentable.

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection because the declared unexpected results clearly overcome any *prima facie* case of obviousness.

Conclusion

Applicants submit that every issue raised by the Office Action mailed October 4, 2004 has been addressed and rebutted. Therefore, the present claims define patentable subject matter and are in condition for allowance.

Pursuant to 37 C.F.R. §§1.17 and 1.136(a), Applicants respectfully petition for a one month extension of time for filing a response in connection with the present application. Please charge the required fee of $120 to Deposit Account No. 02-2334.

Attorney Docket No. O/98414 US

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2334 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

Mark W. Milstead
Attorney for Applicants
Registration No. 45,825

Akzo Nobel Pharma Patent Dept.
P.O. Box 318
29160 Intervet Lane
Millsboro, DE 19966
Tel: (302) 933-4034
Fax: (302) 934-4305

MWM